Guidance for Industry

BACPAC I: Intermediates in Drug Substance Synthesis

Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Kasturi Srinivasachar (301) 594-5376 or (CVM) David Newkirk (301) 594-2701.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
November 1998

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

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(Due to the complexity of this draft document, please identify specific comments by line number.)

I. INTRODUCTION

This guidance provides recommendations to sponsors of new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), and abbreviated new animal drug applications (ANADAs), and holders of drug master files (DMFs) or veterinary master files (VMFs) who intend, during the postapproval period, to change (1) the site of manufacture, (2) the scale of manufacture, (3) the equipment, (4) the ***specifications***,[2] and/or (5) the manufacturing process of ***intermediates*** in the synthetic pathway leading to the ***drug substance***.[3]

This guidance defines recommended chemistry, manufacturing and controls tests, and documentation in support of each change. The guidance applies to synthetic drug substances and the synthetic steps involved in the preparation of ***semisynthetic drug substances***. It is limited to structurally well-characterized drug substances for which ***impurities*** can be monitored at the levels recommended. The guidance covers changes as follows: (1) site, scale, and equipment

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[1] This guidance has been prepared by the Bulk Actives Postapproval Changes (BACPAC) Working Group of the Drug Substance Technical Committee operating under the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) with participation by the Center for Veterinary Medicine (CVM) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on postapproval changes for the manufacture of intermediates in drug substance synthesis. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] Terms in bold italics are defined in the glossary.

[3] The FDA solicited early input on this topic via a public meeting sponsored by the American Association of Pharmaceutical Scientists in conjunction with the FDA. The meeting, held March 25-27, 1997, provided a forum for FDA to hear the public's opinions on postapproval changes in the manufacture of drug substances.

changes involving the synthetic steps up to and including the step that produces the ***final intermediate***, (2) specification changes for raw materials, ***starting materials***, and intermediates except the final intermediate, and (3) manufacturing process changes involving the synthetic steps up to and including the final intermediate.[4] Postapproval changes affecting (1) synthetic peptides, (2) oligonucleotides, (3) radiopharmaceuticals, or (4) drug substances derived exclusively by isolation from natural sources or produced by procedures involving biotechnology are not addressed in this document.

This guidance sets forth information that should be provided to the Center for Drug Evaluation and Research (CDER) or the Center for Veterinary Medicine (CVM) to ensure continuing drug substance quality and ***drug product*** quality and performance characteristics for specified postapproval changes. This guidance does not comment on or otherwise affect compliance or inspection documentation that has been defined by the Office of Compliance or FDA's Office of Regulatory Affairs. This guidance does not affect any postapproval changes other than the changes specified. For changes not addressed in this guidance or where alternative filing mechanisms may be appropriate, applicants should contact the appropriate CDER or CVM review division(s) or consult other CDER or CVM guidances to obtain information about tests and application documentation. For veterinary products, an alternative administrative procedure may also be available for reporting postapproval changes.

FDA regulations at 21 CFR 314.70(a) state that applicants may make changes to an approved application in accordance with a guideline, notice, or regulation published in the *Federal Register* that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report). This guidance provides for less burdensome notice of certain postapproval changes within the meaning of § 314.70(a). For changes filed as a *changes being effected supplement* (21 CFR 314.70(c) and 514.8(d)(3)), the FDA may, after a review of the supplemental information, decide that the changes are not approvable.

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (FDAMA).[5] Section 116 of FDAMA amended the Food, Drug, and Cosmetic Act by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved human and animal drug application and for distributing a drug product made with such change. The FDA is currently preparing a proposed rule to amend its regulations (21 CFR 314.70 and 21 CFR 514.8) for supplements and other changes to approved applications to implement the manufacturing changes provision of FDAMA. This draft

[4] Changes to the final intermediate and manufacturing changes after the final intermediate will be covered in a forthcoming BACPAC II guidance.

[5] Pub. L. 105-115

guidance will be revised as and when appropriate to take into consideration the revised regulations in 21 CFR 314.70 and 21 CFR 514.8 when they are finalized.

II. GENERAL CONSIDERATIONS

Any modification to the method of manufacture of a drug substance carries some risk of causing adverse impact, either in the physical properties of the drug substance or in the level or nature of impurities present. The risk of adverse change is generally acknowledged to be greater when a modification occurs near the end of a drug substance manufacturing process rather than the beginning. Also, certain kinds of modifications (e.g., equipment or site changes) are viewed as less likely to result in adverse change than others (e.g., changes in the synthetic route). However, there are no simple rules for determining how much risk is associated with any particular modification. This guidance is limited to changes made up to and including the final intermediate because these early modifications are generally viewed as less likely to have an adverse impact on the drug substance and, consequently, on the finished dosage form. The final intermediate was chosen as the break point in this attempt to categorize risk because

- it is typically the best characterized material in the synthetic scheme except for the drug substance itself, and

- physical properties of the drug substance usually will not be affected by changes made up to that point.

The responsibility for documenting a modification to the manufacturing method for a drug substance may lie with a single party or several parties. Communication among the parties involved regarding the change is important so that the applicant can determine the appropriate filing mechanism. The synthesis of the drug substance should have been fully described, from starting materials to final drug substance, either in a drug application or in one or more master files. If the method of manufacture of the drug substance is described in an application, then documentation of any modification should be filed in an annual report or a supplement to the application, as appropriate. If the method of manufacture is described in a master file, then documentation of the modification should be filed as an amendment(s) to the master file, and all applicants authorized to reference the master file should be notified. Although details of the change may be kept confidential, at a minimum the holder of the master file should inform applicants of the type of filing recommended for their respective drug applications. The applicants should then document in an annual report or a supplement to each affected drug application, as appropriate, that the master file has been amended.

III. ASSESSMENT OF CHANGE

A central tenet of this guidance is that a given change in the drug substance manufacturing process can be adequately assessed by comparing pre- and postchange materials and demonstrating that the postchange material is equivalent to the prechange material (i.e., of the same or better quality, as described below). When equivalence cannot be demonstrated, a prior approval supplement should be submitted by the applicant(s) and the need for qualification of impurities, demonstration of bioequivalence, and assessment of stability should be considered. This document does not call for the submission of stability data or routine stability commitments. However, the stability of some drug products may be affected by small changes in impurities (e.g., in the trace levels of heavy metals). For drug products in which stability problems may potentially occur, the first commercial ***batch*** of drug product made with postchange drug substance should be included in the firm's stability testing program.

Two major factors for determining equivalence in the drug substance are the ***impurity profile*** and physical properties. For the purposes of this guidance, only these factors will be considered. However, other factors that may be important in individual cases should be evaluated to demonstrate equivalence. For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change. There should be no structural changes to the final intermediate or to the drug substance.

A. Equivalence of Impurity Profiles

The impact of manufacturing modifications on the impurity profile is evaluated by determining levels of existing impurities and new impurities. Determining the stage in the manufacturing process at which impurities should be evaluated and establishing the adequacy of the methods used for this purpose are important considerations. Levels of residual solvents and inorganic substances should also be considered during evaluation of the impurity profile.

Impurities may be evaluated in ***isolated intermediates*** immediately following the process step in which the manufacturing modification is made. If it can be shown that the impurity profile of an isolated intermediate following the modified step is equivalent (as defined below), it will be accepted that the impurity profile of the drug substance is not affected by the modification. If equivalence cannot be demonstrated at the isolated intermediate immediately following the change, the impurity search can be extended to the next downstream intermediate and the evaluation process repeated until the final intermediate is reached. The Agency recognizes that it may not always be possible to establish equivalence prior to or at the final intermediate. For example, sufficient analytical methods may not be available or cannot be developed, or ***historical data*** may not exist in some cases. When it is not feasible to evaluate impurities in intermediates or equivalence cannot be demonstrated at these stages, the testing can be carried out on the drug substance itself.

The method used to evaluate the change should be adequate for quantitating both existing and new impurities at the recommended levels. Development of new analytical methods may be necessary. When new methods are developed for this purpose, validation data should be provided. The same analytical method should be used when comparing impurity levels in pre- and postmodification batches.

The level of impurities should be assessed by comparing three postmodification batches to the range of historical data from ten premodification commercial batches. This analysis should normally be carried out soon after manufacture. However, retained samples may be used for the comparison provided there is no trend toward the level of any impurity increasing over time.

The impurity profile will be considered equivalent after a given change if at least three postmodification batches of either an isolated intermediate or the drug substance are evaluated and the test data demonstrate that for:

1. An intermediate:

   a. No new impurity is observed at or above 0.1 percent. This impurity level is judged to be appropriate for intermediates leading to either low-dose or high-dose drugs. Further reduction of impurity levels will frequently occur in the subsequent step or steps prior to drug substance formation.

   b. Existing impurities, including residual organic solvents, are at or below the upper statistical limit[6] of historical data.

   c. ***Total impurities*** are at or below the upper statistical limit of historical data.

2. A drug substance:

   a. No new impurity is observed at or above the threshold for qualification of impurities as described in the International Conference on Harmonisation (ICH) guidance *Q3A Impurities in*

[6] See definition of *historical data* in the glossary.

New Drug Substances.[7] For veterinary products, the threshold currently is being considered.[8]

b. Existing impurities, including residual organic solvents, are within the stated limits or, if not specified, are at or below the upper statistical limit of historical data.

c. Total impurities are within the stated limits or, if not specified, are at or below the upper statistical limit of historical data.

Additional principles regarding equivalence of impurity profiles are outlined below.

- Equivalence of the impurity profile may be established by testing any isolated intermediate following the change, including the final intermediate, or the drug substance.

- ***In situ intermediates*** are generally not appropriate for demonstrating equivalence.

- The batches of the intermediate or drug substance used for testing should be synthesized using exclusively the material that has been subjected to the change(s) without blending with prechange material.

- When a manufacturing change is made to an outsourced intermediate, equivalence can be established by either the vendor or the customer. However, in addition to assessing equivalence of the impurity profile, adequate release or acceptance testing, as appropriate, should be carried out.

- Changes in process, specifications, or equipment may be evaluated using data from ***pilot scale*** batches. If equivalence is demonstrated by using pilot batches, the first commercial batch should also be evaluated for equivalence. The resulting commercial batch data should be kept on file at the manufacturing site. When equivalence cannot be demonstrated at commercial scale, the reviewing division should be contacted.

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[7] Although this ICH guidance is intended for registration applications of new drug substances, the qualification thresholds established are appropriate for evaluating impurity profiles for BACPAC I.

[8] A draft guidance for industry on impurities in new veterinary drug substances is under development as part of the International Cooperation on Harmonisation of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH). The notice announcing the availability of this draft guidance is expected to publish shortly.

- Additional purification procedures (or repetition of an existing procedure on a routine basis) to achieve equivalence with prechange material after the final intermediate are not covered under BACPAC I. However, modified purification procedures prior to the final intermediate can be filed under BACPAC I (see section IV.C for process changes and section IV.D for multiple changes).

B. Equivalence of Physical Properties

In general, physical properties of the drug substance are not likely to be affected by changes made before the final intermediate because most synthetic schemes involve dissolution of the crude drug substance in a suitable solvent before the drug substance is isolated by crystallization or precipitation. This ***final solution step***, and not a preceding step, usually determines the physical properties of the drug substance. Generally, the only way changes before the final intermediate can affect the physical properties of the drug substance is by carryover of new impurities or higher levels of existing impurities into the final solution step. Although minor differences in the impurity profile at this stage are unlikely to cause physical property modifications to the drug substance, the possibility of such changes in physical properties should be considered. Consequently, physical properties of the drug substance, when they are relevant to finished dosage form performance, should be evaluated unless equivalence of the impurity profile can be demonstrated prior to or at the final intermediate.

Generally, only two physical properties of the drug substance, morphic form and particle size, are considered critical for evaluation of equivalence. However, other physical properties may be important in individual cases. The physical properties of the drug substance will be considered equivalent after a given change if at least three postmodification batches of the drug substance are prepared and the data demonstrate:

- Conformance to established acceptance criteria for morphic form or, where acceptance criteria do not exist, the isolation of the same form or mixture of forms within the range of historical data, and

- Conformance to historical particle size distribution profile.

The BACPAC Decision Tree (Attachment A) incorporates the approaches described above for the evaluation of impurity profiles and physical properties and is a general guide to the assessment of change.

IV. TYPES OF CHANGE

A. Site, Scale, and Equipment Changes

The manufacturing site, scale of manufacture, and manufacturing equipment changes discussed in this section do not include any modifications to the synthetic pathway (i.e., the same starting material(s), intermediates, solvents, and reagents are involved). Adjustments in process parameters should be limited to those needed to accommodate new equipment. Under these constraints, the changes in this category should not usually give rise to different impurity profiles for either the intermediates following the change or the drug substance.

Concurrent or multiple site, scale, and equipment changes may be made. The test documentation should be the sum of the recommendations for individual changes, and the filing mechanism should be the most restrictive.

1. Site Changes

Site changes consist of changes in location of the site of manufacture of intermediates, including the final intermediate, for both company-owned and contract manufacturing facilities. The new site, which may be within a single facility, within a contiguous campus, or in a different campus, should have similar environmental controls. Site changes can involve the addition of new contract manufacturing facilities or the relocation of manufacturing facilities approved in the referenced application(s). Transfer of an additional manufacturing step to a facility approved for other manufacturing steps should be filed as a site change. New manufacturing facilities should operate in accordance with the principles of current Good Manufacturing Practice.

Site changes within a single facility that fall within the scope of sections IV.A and IV.A.1 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out. However, ***installation qualification (IQ)*** and ***operation qualification (OQ)*** information should be retained in-house and is subject to FDA's review at its discretion.

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

- The name and address of the new facility.
- A concise description of the manufacturing steps being transferred, a summary (with ***justification***) of any variation in equipment or process

parameters, and a statement that the synthetic pathway is identical at the new site.

- Evaluation of the impurity profile and physical properties:

  A report on the evaluation of changes in impurities that includes a description of analytical methods, data on at least three batches made at the new site, historical data for comparison, and a description of the source of the historical data. Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose.

  If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is needed.

  If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, the change should not be implemented until a supplement for the modification has been approved. When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered. The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

- A Certificate of Analysis from the manufacturer for each outsourced intermediate affected by the site change.

Filing Documentation:

- Annual Report if the site change does not involve the final intermediate and the new site is owned either by the applicant or by a contract manufacturer previously approved in the application for the manufacturing step(s) being transferred.

- Changes being effected supplement if

  - The site change involves the final intermediate,

- The new site is owned by a contract manufacturer not previously approved for this application, or

- The new site is owned by a contract manufacturer approved for this application but not approved for the manufacturing step(s) being transferred.

2. Scale Changes

Scale changes include increases and decreases in the batch size of intermediates including the final intermediate. No attempt is made to classify scale changes according to the magnitude of the change. Equipment of a different capacity may be used in conjunction with these changes. Adjustments in process parameters should be limited to those needed to accommodate new equipment.

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

- A concise description of the change, a summary with justification of any variation in equipment or process parameters, and a statement that the synthetic pathway is identical.

- Evaluation of the impurity profile and physical properties:

  A report on the evaluation of changes in impurities that includes a description of analytical methods, data on at least three batches made at the new scale, historical data for comparison, and a description of the source of the historical data. Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose.

  If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is needed.

  If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, the change should not be implemented until a supplement for the modification has been approved. When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the

dosage form should be considered. The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

- A Certificate of Analysis from the supplier for each outsourced intermediate affected by the scale change.

Filing Documentation:

- Annual Report.

3. Equipment Changes

Generally, equipment changes are accompanied by other changes (e.g., process). In the rare instances when equipment changes alone are made, the following test and filing documentation are recommended.

A change to new equipment that is not significantly different from that previously used with no modifications to process parameters need not be filed with the Agency, and equivalence testing as described in this document need not be carried out. However, installation qualification (IQ) and operation qualification (OQ) information should be retained in-house and is subject to FDA's review at its discretion.

If the new equipment is significantly different from that previously used, the potential for a change in the impurity profile exists even when there are no modifications to process parameters. Examples include switching from glass to metal reactors or changing the method of agitation for a step that depends on the mixing of heterogeneous materials. A significant change of equipment should be filed as an amendment(s) to the master file(s) and/or in an annual report, as appropriate, and documented as described for scale changes.

B. Specification Changes

Specification changes can be made for raw materials (solvents and reagents), starting materials, or intermediates in a synthetic process. Specification changes for the final intermediate are not included in this guidance.

1. Specification Changes Made to Comply with Compendial Changes

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

- A description of the change with appropriate validation data for any new analytical methods used.
- An updated specification(s).

Filing Documentation:

- Annual Report.

2. Specification Changes That Provide Greater Assurance of Quality

Examples:

- Tightening of acceptance criteria.
- Replacing an existing analytical method with an improved method.
- Revised specification(s) associated exclusively with improved analytical methods.

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

- Rationale for the proposed change, a description of new analytical methods including a discussion of improvements over existing methods, and validation data.
- Certificate of Analysis or batch release data for raw material or intermediate, as appropriate.
- An updated specification(s).

Filing Documentation:

- Annual Report.

3. Other Specification Changes

Examples:

- Relaxing acceptance criteria.
- Deleting a test.
- Replacing an existing analytical method with a new method that does not qualify as an improvement.
- Revised specification(s) associated with a change in supplier/grade of starting materials, reagents, or solvents.

In general, equivalence should be demonstrated using material that challenges the specification change. For example, if an assay acceptance criterion has been relaxed from a 98–102 percent range to a 90–102 percent range, equivalence should be demonstrated for batches made using raw material with an assay value near the new lower limit (i.e., 90 percent).

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

- A description of and justification for the change.
- Evaluation of the impurity profile and physical properties:

  A report on the evaluation of changes in impurities that includes a description of analytical methods, data on at least three batches made using material that justifies the revised specification(s), historical data for comparison, and a description of the source of the historical data. Validation data should be provided for new test methods and also for existing methods, if their use is being extended beyond their original purpose.

  If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is needed.

  If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, the change should not be implemented until a supplement for the modification

has been approved. When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered. The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

- Certificates of Analysis for raw materials, solvents, or outsourced intermediates and batch release data for intermediates, as appropriate.

- An updated specification(s).

Filing Documentation:

- Changes being effected supplement. If solvent or reagent changes can be justified without the need to generate test data, then filing in an annual report may be appropriate. In those situations, the appropriate review division(s) should be contacted for concurrence.

C. Manufacturing Process Changes

This category encompasses a wide range of process-related changes that may involve the use of different equipment and a change of scale. A new specification(s) may be necessary when different solvents, reagents, starting materials, or intermediates are involved (see also section IV.B Specification Changes). Process changes that result in the formation of a different final intermediate are outside the scope of this guidance.

1. Changes That Do Not Involve New Starting Materials or Intermediates

Examples include changes in solvents, reagents, process parameters, or purification procedures in one or more steps of the synthetic procedure.

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

- Description of change.

- Specification(s) for new reagents and solvents and Certificates of Analysis from the suppliers, if applicable.

- Evaluation of the impurity profile and physical properties:

A report on the evaluation of changes in impurities that includes a description of analytical methods, data on at least three batches made using material produced by the changed process, historical data for comparison, and a description of the source of the historical data. Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose.

If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is needed.

When a new solvent is introduced into the synthetic process, the possibility of carryover into the drug substance should be assessed. Tests and acceptance criteria should be established as appropriate. The level of the new solvent in the drug substance should be below its ICH Q3C Option 1 limit.[9] If the level of the new solvent in an intermediate is at or below the ICH Q3C Option 1, no testing of the drug substance is needed.[10]

If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, the change should not be implemented until a supplement for the modification has been approved. When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered. The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

- A Certificate of Analysis from the supplier for each outsourced intermediate affected by the process change.

Filing Documentation:

- Changes being effected supplement.

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[9] International Conference on Harmonisation; *Q3C Impurities: Residual Solvents*; *Federal Register*, December 24, 1997 (62 FR 67377). Although this ICH guidance does not apply to existing marketed drug products, the Option 1 limits are appropriate for evaluating residual solvent levels for BACPAC I.

[10] For veterinary drug substances, contact the Division of Manufacturing Technologies, HFV-140, Center for Veterinary Medicine, FDA .

2. Changes in the Route of Synthesis in One or More Steps Involving Different Starting Materials and/or Intermediates (except the final intermediate)

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

- Description of the change with details of the new synthetic procedure and any in-process controls.
- Appropriate structural characterization data for intermediates.
- Specification(s) for any new starting materials and/or intermediates.
- Evaluation of the impurity profile and physical properties:

  A report on the evaluation of changes in impurities that includes a description of analytical methods, data on at least three batches made using material produced by the changed process, historical data for comparison, and a description of the source of the historical data. Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose.

  If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is needed.

  When a new solvent is introduced into the synthetic process, the possibility of carryover into the drug substance should be assessed. Tests and acceptance criteria should be established as appropriate. The level of the new solvent in the drug substance should be below its ICH Q3C Option 1 limit. If the level of the new solvent in an intermediate is at or below the ICH Q3C Option 1, no testing of the drug substance is needed.

  If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, these changes should not be implemented until a supplement for the modification has been approved. In such cases, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be

considered. The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

- A Certificate of Analysis from the supplier for each outsourced intermediate affected by the process change.

Filing Documentation:

- Prior approval supplement. For route changes very early in the synthetic scheme where equivalence is determined soon after the change, submission as a changes being effected supplement may be justified. In those situations, the appropriate review division(s) should be contacted for concurrence prior to filing.

3. Changes in Which an Intermediate Is Redefined as a Starting Material

This change may be in response to an increase in commercial availability of the proposed starting material. In general, the specification for the proposed starting material should be more comprehensive (e.g., additional tests and/or tighter acceptance criteria) than for the intermediate. Comparative data should be provided to demonstrate equivalence of a downstream intermediate or of the drug substance using the proposed starting material from a new source. Redefinition of a final intermediate as a starting material is not covered under BACPAC I.

Test Documentation (filed as an amendment(s) to the master file(s) and/or in an annual report or supplement to the application(s), as appropriate):

- Rationale for the proposed change and overview of current synthetic procedure.

- A new or revised specification, a description of new or revised analytical methods for the redefined starting material, and, if appropriate, additional or tightened acceptance criteria and in-process controls for downstream intermediates.

- A list of sources (including commercial vendors and contract manufacturers) of the redefined starting material,.

- An outline of the change-control protocol that has been or will be followed when establishing the suitability of a new supplier or when the existing supplier's process is changed.

- Evaluation of the impurity profile and physical properties:

  A report on the evaluation of changes in impurities that includes a description of analytical methods, data on at least three batches made using material that justifies the new or revised specification(s), historical data for comparison, and a description of the source of the historical data. Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose.

  If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is needed.

  When a new solvent is introduced into the synthetic process, the possibility of carryover into the drug substance should be assessed. Tests and acceptance criteria should be established as appropriate. The level of the new solvent in the drug substance should be below its ICH Q3C Option 1 limit. If the level of the new solvent in an intermediate is at or below the ICH Q3C Option 1, no testing of the drug substance is needed.

  If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, the change should not be implemented until a supplement for the modification has been approved. When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered. The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

- Certificates of Analysis from the supplier for the proposed starting material.

Filing Documentation:

- Changes being effected supplement.

D. Multiple Changes

Multiple changes are those that involve various combinations of the changes described in sections IV.A, B, and C. The test documentation should be the sum of the recommendations for individual changes and the filing mechanism the most restrictive. For example, a change in the route of synthesis (prior approval supplement) and change in the manufacturing site to a new contract manufacturer (changes being effected supplement) should be filed as a prior approval supplement, and the applicant should provide the listed test documentation for both changes.

REFERENCES

Food and Drug Administration (FDA), *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, Center for Drugs and Biologics, February 1987.

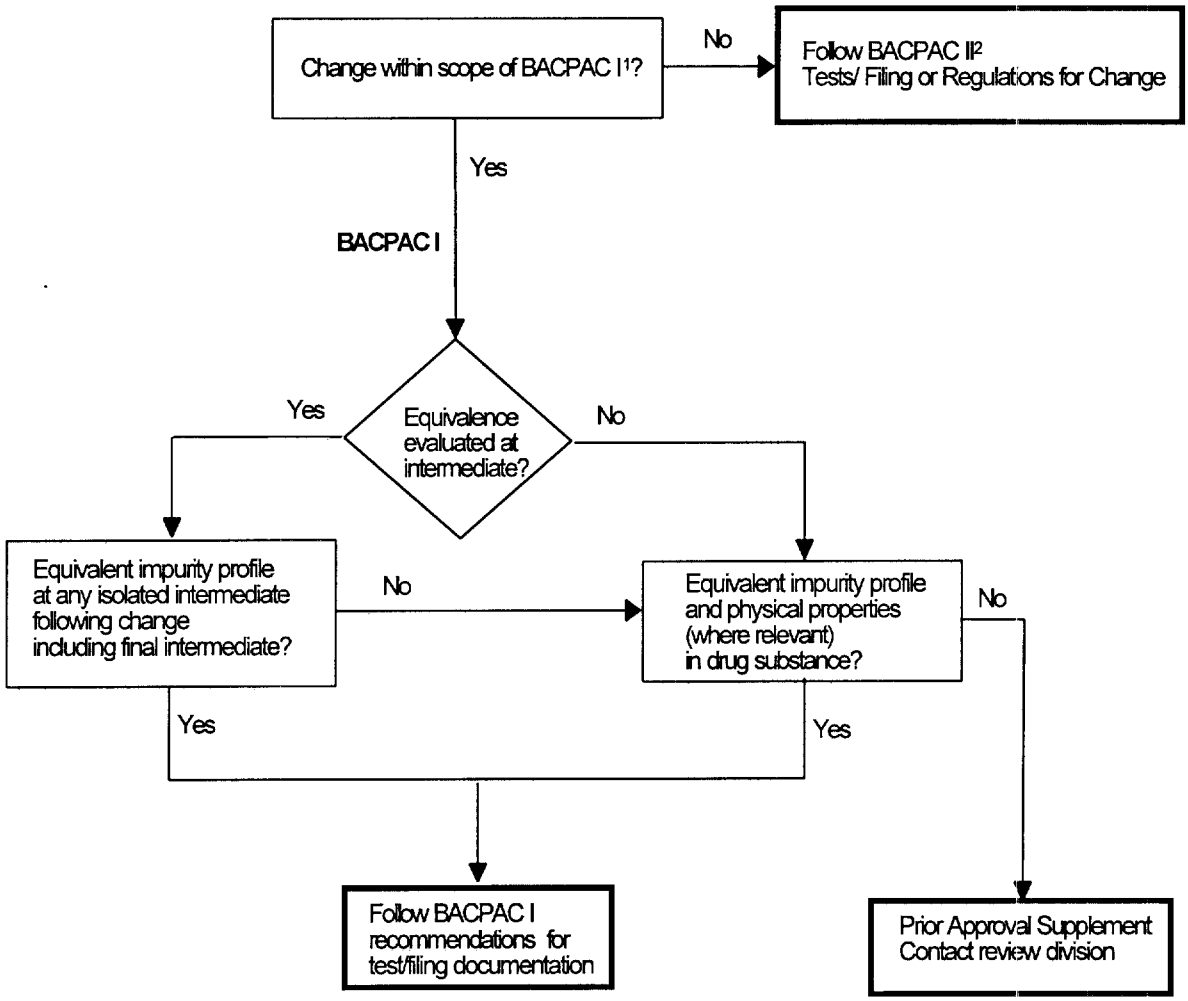
FDA, *Immediate Release Solid oral Dosage Forms — Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (SUPAC-IR)*, November 1995.

International Conference on Harmonisation (ICH), *Q3A Impurities in New Drug Substances*, January 1996.

ICH, *Q3C Impurities: Residual Solvents*, *Federal Register*, December 24, 1997 (62 FR 67377).

ICH, *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Draft)*, November 25, 1997 (62 FR 62889).

561 # ATTACHMENT A — BACPAC DECISION TREE



562 [1] Site, scale, and equipment changes involving the synthetic steps up to and including the step that produces the final
563 intermediate; specification changes for raw materials, starting materials, and intermediates except the final intermediate;
564 manufacturing process changes involving the synthetic steps up to and including the step that produces the final
565 intermediate.

566 [2] Forthcoming guidance

ATTACHMENT B — GLOSSARY OF TERMS

Batch: A specific quantity of an intermediate or drug substance intended to have uniform character and quality, within specified limits, and produced according to a single manufacturing order during the same cycle of manufacture. A batch may also mean a specific quantity of material or drug substance processed in one process or series of processes so that it could be expected to be homogeneous (21 CFR 210.3(b)(2)).

Drug Product: A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)(4)).

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Final Intermediate: For the purposes of this guidance, the last compound synthesized before the reaction that produces the drug substance. The final step forming the new drug substance must involve covalent bond formation; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

Final Solution Step: The solution from which the drug substance is isolated in pure form by either crystallization or precipitation. Where the purification procedure for the crude drug substance involves several crystallization or precipitation steps, final solution step refers only to the last of these steps.

Historical Data: Data on impurities or physical attributes from 10 recent batches representative of the established process. The upper statistical limit of an impurity is generally based on the mean plus three times the standard deviation. (The appropriate review division(s) should be contacted for concurrence in those rare instances (e.g., low-volume drug substances) where evaluation of historical data is based on <10 batches.)

Impurity: Any component of the drug substance that is not the entity defined as the drug substance (ICH Q3A).

Impurity profile: A description of the identified and unidentified impurities present in a drug substance (ICH Q3A).

In Situ Intermediate: An intermediate that is not isolated. It is normally, but not necessarily, in solution (*Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*).

Installation Qualification (IQ): The documented verification that all key aspects of the equipment and ancillary systems installations adhere to the approved design intentions (plans) and that the recommendations of the manufacturer are suitably considered.

Intermediate: A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes a drug substance (ICH Q3A).

Isolated Intermediate: An intermediate that is obtained as the product after work-up of a reaction step in the synthetic scheme for the drug substance. The isolation or purification procedure should be part of the validated process. An aliquot of a reaction product that is worked up and/or purified for purposes of characterization does not constitute an isolated intermediate.

Justification: Reports containing scientific data and expert professional judgement to substantiate decisions (*SUPAC IR, Immediate Release Solid Oral Dosage Forms, Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*).

Method Validation: The process of proving that an analytical test procedure is effective for its intended use.

Operational Qualification (OQ): The documented verification that the equipment and ancillary systems perform as intended throughout anticipated operating ranges (i.e., pressures, temperatures, times).

Pilot Scale: The manufacture of a bulk drug substance or intermediate on a reduced scale by processes representative of and simulating that to be applied on a larger, commercial manufacturing scale.

Polymorphism: The occurrence of different crystalline forms of the same drug substance (ICH Q3A).

Process Validation: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics.

Semisynthetic Drug Substance: A drug substance produced by fermentation and synthesis or synthesized from a precursor or structural element of natural origin (e.g., a natural product of natural or plant origin).

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance should conform to be considered acceptable for its intended use. *Conformance to specifications* means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant (ICH draft guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*).

Starting Material: A material used in the synthesis of a drug substance that is incorporated as an element into the structure of an intermediate and/or of the drug substance. Starting materials are usually available from commercial sources, and their chemical and physical properties, structure, and impurity profile are well defined in the chemical literature.

Total Impurities: The sum of all impurities observed above the limit of quantitation.